



Life Science Alliance

Chitinase1 Regulates Pulmonary Fibrosis by Modulating TGF- β /Smad7 Pathway via TGFBRAP1 and FOXO3

Chang-Min Lee, Jin Park, Jae Hyun Lee, Emily Chen, Suchitra Kamle, Bing Ma, Bedia Akosman, Roberto Cortez, Chuan He, Yang Zhou, Erica Herzog, Changwan Ryu, Xueyan Peng, Ivan Rosas, Sergio Poli, Carol Feghali Bostwick, Augustine Choi, Jack Elias, and Chun Lee

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Scientific Editor: Andrea Leibfried

Transaction Report:

(Note: With the exception of the correction of typographical or spelling errors that could be a source of ambiguity, letters and reports are not edited. The original formatting of letters and referee reports may not be reflected in this compilation.)

Please note that the manuscript was previously reviewed at another journal and the reports were taken into account in the decision-making process at Life Science Alliance. Since the original reviews are not subject to Life Science Alliance's transparent review process policy, the reports and author response cannot be published.

February 19, 2019

Re: Life Science Alliance manuscript #LSA-2019-00350-T

Dr. Chun Geun Lee
Brown University
Molecular Microbiology and Immunology
185 Meeting St
Providence, RI 02912

Dear Dr. Lee,

Thank you for transferring your manuscript entitled "Chitinase1 Regulates Pulmonary Fibrosis by Modulating TGF- β Signaling and SMAD7 Expression via TGFBRAP1 and FOXO3" to Life Science Alliance. The manuscript was assessed by expert reviewers at another journal before, and the editors transferred those reports to us with your permission.

The reviewers pointed out that your work corroborates and extends your previous study. They noted that clarifications and further insight would be needed. Based on the reports already at hand, we would like to invite you to submit a revised version of this work. We would expect a point-by-point response to the concerns raised by the reviewers and accordingly further discussion and inclusion of additional data. More specifically, points 1-4 of reviewer #1 should get addressed (point 4 via text changes); points on Van Dyken et al., 2017, on the effects being due to TGFbR expression/TGFb1 exposure (reviewer #2) should get addressed and the correlation of CHIT1 with disease progression should get revisited (reviewer #2); other possible mechanisms should get considered and points 1-3 of reviewer #3 should get addressed. Further reaching insight (points 5, 7, 8 of reviewer #1; point 4 of reviewer #3) is not needed for publication in LSA.

To upload the revised version of your manuscript, please log in to your account:
<https://lsa.msubmit.net/cgi-bin/main.plex>

You will be guided to complete the submission of your revised manuscript and to fill in all necessary information.

We would be happy to discuss the individual revision points further with you should this be helpful.

While you are revising your manuscript, please also attend to the below editorial points to help expedite the publication of your manuscript. Please direct any editorial questions to the journal office.

The typical timeframe for revisions is three months. Please note that papers are generally considered through only one revision cycle, so strong support from the referees on the revised version is needed for acceptance.

Thank you for this interesting contribution to Life Science Alliance. We are looking forward to receiving your revised manuscript.

Sincerely,

Andrea Leibfried, PhD
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A. THESE ITEMS ARE REQUIRED FOR REVISIONS

- A letter addressing the reviewers' comments point by point.
- An editable version of the final text (.DOC or .DOCX) is needed for copyediting (no PDFs).
- High-resolution figure, supplementary figure and video files uploaded as individual files: See our detailed guidelines for preparing your production-ready images, <http://www.life-science-alliance.org/authors>
- Summary blurb (enter in submission system): A short text summarizing in a single sentence the study (max. 200 characters including spaces). This text is used in conjunction with the titles of papers, hence should be informative and complementary to the title and running title. It should describe the context and significance of the findings for a general readership; it should be written in the present tense and refer to the work in the third person. Author names should not be mentioned.

B. MANUSCRIPT ORGANIZATION AND FORMATTING:

Full guidelines are available on our Instructions for Authors page, <http://www.life-science-alliance.org/authors>

We encourage our authors to provide original source data, particularly uncropped/-processed electrophoretic blots and spreadsheets for the main figures of the manuscript. If you would like to add source data, we would welcome one PDF/Excel-file per figure for this information. These files will be linked online as supplementary "Source Data" files.

*****IMPORTANT:** It is Life Science Alliance policy that if requested, original data images must be made available. Failure to provide original images upon request will result in unavoidable delays in publication. Please ensure that you have access to all original microscopy and blot data images before submitting your revision.***

April 25, 2019

RE: Life Science Alliance Manuscript #LSA-2019-00350-TR

Dr. Chun Geun Lee
Brown University
Molecular Microbiology and Immunology
185 Meeting St
Providence, RI 02912

Dear Dr. Lee,

Thank you for submitting your revised manuscript entitled "Chitinase1 Regulates Pulmonary Fibrosis by Modulating TGF- β /Smad7 Pathway via TGFBRAP1 and FOXO3". We appreciate the introduced changes and would be happy to publish your paper in Life Science Alliance pending final minor revisions:

- We note that the point on "the correlation of CHIT1 with disease progression (reviewer #2)" was not revisited. Could you please address this point that relates to the comment on Figure 7C, where only 5 out of 18 patients have a significant elevation of CHIT1 activity.
- Please update the callouts to Figure 2 panels in the text. You still refer to Figure 2B and C when describing the effect on Smad and ERK levels. The results shown in new Figure 2B and C are not described in the main text. No callouts are present to Figure 2D and 2E.
- Main text, page 10: you removed the data from COPD patients from Figure 6A but still refer to these data in the text.
- The COPD patients are still mentioned on the first page of the Appendix: "Table S2. Demographic feature of COPD and IPF patients and controls used in this study". They are also mentioned in the Materials and Methods section, page 21.
- Please address point 9 from reviewer #1 and correct the typo in the first paragraph of the introduction: "... is a key driver of scaring... should be "... is a key driver of scarring...".
- Our routine image analysis revealed a potential splice site in Figure 3A, b-actin. In case the blot was spliced please indicate this with a stippled line. Please also provide the unmodified source data for this panel.
- Figure 7D: please specify the number of patients analysed in the figure legend.
- Figure legends: please indicate the statistical test used to generate the respective p-values.
- Please move the Supplemental figure legends to the main manuscript text.
- Fig. S1: please define the bars and error bars.

- Fig. S3: please define the meaning of "*" " in the legend.

If you are planning a press release on your work, please inform us immediately to allow informing our production team and scheduling a release date.

To upload the final version of your manuscript, please log in to your account:

<https://lsa.msubmit.net/cgi-bin/main.plex>

You will be guided to complete the submission of your revised manuscript and to fill in all necessary information. Please get in touch in case you do not know or remember your login name.

To avoid unnecessary delays in the acceptance and publication of your paper, please read the following information carefully.

A. FINAL FILES:

These items are required for acceptance.

-- An editable version of the final text (.DOC or .DOCX) is needed for copyediting (no PDFs).

-- High-resolution figure, supplementary figure and video files uploaded as individual files: See our detailed guidelines for preparing your production-ready images, <http://www.life-science-alliance.org/authors>

-- Summary blurb (enter in submission system): A short text summarizing in a single sentence the study (max. 200 characters including spaces). This text is used in conjunction with the titles of papers, hence should be informative and complementary to the title. It should describe the context and significance of the findings for a general readership; it should be written in the present tense and refer to the work in the third person. Author names should not be mentioned.

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****Submission of a paper that does not conform to Life Science Alliance guidelines will delay the acceptance of your manuscript.****

****It is Life Science Alliance policy that if requested, original data images must be made available to the editors. Failure to provide original images upon request will result in unavoidable delays in publication. Please ensure that you have access to all original data images prior to final submission.****

****The license to publish form must be signed before your manuscript can be sent to production. A link to the electronic license to publish form will be sent to the corresponding author only. Please**

take a moment to check your funder requirements.**

Reviews, decision letters, and point-by-point responses associated with peer-review at Life Science Alliance will be published online, alongside the manuscript. If you do want to opt out of this transparent process, please let us know immediately.

Thank you for your attention to these final processing requirements. Please revise and format the manuscript and upload materials within 7 days.

Thank you for this interesting contribution, we look forward to publishing your paper in Life Science Alliance.

Sincerely,

Andrea Leibfried, PhD
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Editorial comments:

- We note that the point on "the correlation of CHIT1 with disease progression (reviewer #2)" was not revisited. Could you please address this point that relates to the comment on Figure 7C, where only 5 out of 18 patients have a significant elevation of CHIT1 activity.

: The reviewer's comment has been addressed in the discussion section in conjunction with Reviewer 1's comments (#4 of reviewer 1's comment in prior response letter) on the use of end stage lungs from the patients with IPF. Since we also noted more prominent changes of CHIT1/SMAD in the lungs rather than serum although they are all statistically significant, the use of CHIT activity and expression both in serum and lung could be a potential biomarker to predict disease severity and prognosis of IPF and SSc-ILD. This change has been made in the main text on pages 16-17 in the revised manuscript.

- Please update the callouts to Figure 2 panels in the text. You still refer to Figure 2B and C when describing the effect on Smad and ERK levels. The results shown in new Figure 2B and C are not described in the main text. No callouts are present to Figure 2D and 2E.

: Corrected.

- Main text, page 10: you removed the data from COPD patients from Figure 6A but still refer to these data in the text.

: Corrected.

- The COPD patients are still mentioned on the first page of the Appendix: "Table S2. Demographic feature of COPD and IPF patients and controls used in this study". They are also mentioned in the Materials and Methods section, page 21.

: Corrected

- Please address point 9 from reviewer #1 and correct the typo in the first paragraph of the introduction: "... is a key driver of scaring... should be "... is a key driver of scarring...".

: In response to the reviewer's comment, the text has been tone downed as " -- is a potent regulator of scarring human diseases ---" .

- *Our routine image analysis revealed a potential splice site in Figure 3A, b-actin. In case the blot was spliced please indicate this with a stippled line. Please also provide the unmodified source data for this panel.*

: No blots were spliced. Unmodified source data is provided as a pdf file

- *Figure 7D: please specify the number of patients analysed in the figure legend.*

: Total number of patients (n=56) with median (n=28) has been indicated in the figure legend

- *Figure legends: please indicate the statistical test used to generate the respective p-values.*

: Statistical tests are included in the figure legends

- *Please move the Supplemental figure legends to the main manuscript text.*

:

The supplemental figure legends are included in the main text as suggested.

- *Fig. S1: please define the bars and error bars.*

: Error bars have been defined.

- *Fig. S3: please define the meaning of "*" in the legend.*

: defined as *p<0.05.

April 30, 2019

RE: Life Science Alliance Manuscript #LSA-2019-00350-TRR

Dr. Chun Geun Lee
Brown University
Molecular Microbiology and Immunology
185 Meeting St
Providence, RI 02912

Dear Dr. Lee,

Thank you for submitting your Research Article entitled "Chitinase1 Regulates Pulmonary Fibrosis by Modulating TGF- β /Smad7 Pathway via TGFBRAP1 and FOXO3". It is a pleasure to let you know that your manuscript is now accepted for publication in Life Science Alliance. Congratulations on this interesting work.

The final published version of your manuscript will be deposited by us to PubMed Central upon online publication.

Your manuscript will now progress through copyediting and proofing. It is journal policy that authors provide original data upon request.

Reviews, decision letters, and point-by-point responses associated with peer-review at Life Science Alliance will be published online, alongside the manuscript. If you do want to opt out of this transparent process, please let us know immediately.

*****IMPORTANT:** If you will be unreachable at any time, please provide us with the email address of an alternate author. Failure to respond to routine queries may lead to unavoidable delays in publication.***

Scheduling details will be available from our production department. You will receive proofs shortly before the publication date. Only essential corrections can be made at the proof stage so if there are any minor final changes you wish to make to the manuscript, please let the journal office know now.

DISTRIBUTION OF MATERIALS:

Authors are required to distribute freely any materials used in experiments published in Life Science Alliance. Authors are encouraged to deposit materials used in their studies to the appropriate repositories for distribution to researchers.

You can contact the journal office with any questions, contact contact@life-science-alliance.org

Again, congratulations on a very nice paper. I hope you found the review process to be constructive and are pleased with how the manuscript was handled editorially. We look forward to future exciting submissions from your lab.

Sincerely,

Andrea Leibfried, PhD
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